201-14382

NCIC HPV
Sent by: Mary-Beth Weaver

04/01/2003 02:42 PM

To: NCIC HPV, moran.matthew@epa.gov
cc:
cc:
Subject: Environmental Defense comments on Anethole

Richard_Denison@environmentaldefense.org on 04/01/2003 11:46:20 AM

To: oppt.ncic@epamail.epa.gov, hpv.chemrtk@epamail.epa.gov, Rtk Chem/DC/USEPA/US@EPA, Karen Boswell/DC/USEPA/US@EPA, tadams@therobertsgroup.net
cc: lucierg@msn.com, rdenison@environmentaldefense.org, kflorini@environmentaldefense.org

Subject: Environmental Defense comments on Anethole

(Submitted via Internet 4/1/03 to oppt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem.rtk@epa.gov, lucierg@msn.com and tadams@therobertsgroup.net)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for Anethole.

This test plan for anethole was submitted by the Flavor and Fragrance High Production Consortium representing 21 member companies. The test plan covers 2 separate CAS numbers; one for anethole (isomer unspecified) (104-46-1) and the other for trans anethole (4180-23-8). Anetholes are used in a variety of flavor and fragrance applications. They are obtained as or from natural products (e.g., anise oil, pine-derived turpentine) and they are also synthesized. The sponsor claims that most of the anethole obtained, whether as a natural product or from chemical synthesis, is in the trans form. However, no data are presented on the percentages of cis or trans isomers or on the variability in composition of anethole obtained as an extract or as a chemical synthesis product.

The sponsor contends that available data are adequate to fulfill HPV requirements for both CAS numbers. While we agree that existing data for the trans isomer of anethole are adequate for screening level purposes, essentially no studies have been conducted on the unspecified isomer mixture and no justification is provided by the sponsor for grouping both CAS numbers together in a category. It is well known that cis and trans isomers often vary tremendously in their toxic properties, prominent examples being diethylstilbestrol and the polycyclic aromatic hydrocarbons. Therefore, we disagree with the test plan in two major respects: the proposed category is not justified based on the information presented in the test plan; and robust summaries and additional studies are needed on the unspecified anethole isomer mixture. Other comments are listed below:

1. The sponsor states that metabolism of anethole is a detoxification process. However, no information is provided to substantiate this statement. Have toxicology studies been conducted on the major metabolites and/or their intermediates, such as the epoxides?

2. The water solubility of trans anethole appears to be less than that of the unspecified isomer mixture. This suggests that environmental fate and distribution properties might also be different. Therefore, we recommend that fugacity studies be conducted on the unspecified isomer mixture.

3. Ecotoxicity data are available only for trans anethole. Since category formation has not been justified, we recommend that ecotoxicity studies be

conducted on the unspecified isomer mixture as well.

4. Enzyme induction studies reveal that anethole induces cytochrome 1A1. Inducers of this cytochrome often possess toxic properties, including carcinogenicity. Does the sponsor have a good explanation for this finding in their safety assessment? If so, it should be provided.

5. The test plan and robust summaries are somewhat confusing with regard to the identity of the actual test substance that was used for the repeat dose, reproductive and developmental studies, although it appears that trans anethole was used in all of these studies. If true, then we recommend that a combined repeat dose/reproductive/developmental study also be conducted the unspecified isomer mixture. The composition of the test sample should be representative of the commercial product obtained as a natural product and from chemical synthesis.

6. While we agree that no additional genotoxicity studies are needed, we disagree with the statement in the test plan that no mutagenic potential of the anetholes is indicated in the Ames assay. In fact, there were 2 positive studies reported in the robust summaries.

Thank you for this opportunity to comment.

George Lucier, Ph.D.
Consulting Toxicologist, Environmental Defense

Richard Denison, Ph.D.
Senior Scientist, Environmental Defense